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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/825,423	04/03/2001	Patricia C. Weber	ID01152	2057

24265 7590 06/14/2005

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PATENT DEPARTMENT (K-6-1, 1990)
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EXAMINER	
ODELL, LINDSAY T	
ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 06/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/825,423	WEBER ET AL.	
	Examiner	Art Unit	
	Lindsay Odell	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *6 and 18-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 7-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 April 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *31 August 2001*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Application Status

1. In response to the previous Office action, a written restriction requirement (mailed on February 7, 2005), Applicants filed a response received on March 17, 2005. Claims 1-20 are pending in this instant Office action.

Election

2. Applicant's election, without traverse, of Group I, Claims 1-5 and 7-17, drawn to a polypeptide fragment of an HCV helicase derived from subdomain I of the HCV NS3 helicase, in the reply filed on March 17, 2005 is acknowledged. Claims 1-20 are pending in the instant Office action. Claims 1-2, 6, 8-10 and 16-17, drawn to a polypeptide fragment of an HCV helicase, derived from subdomain II of the HCV NS3 helicase; claims 1-2, 10 and 16-17, drawn to a polypeptide fragment of an HCV helicase protein, derived from subdomain III of the HCV NS3 helicase protein; and claims 18-20 are withdrawn as non-elected inventions. Claims 1-5 and 7-17, drawn to a polypeptide fragment of an HCV helicase derived from subdomain I of the HCV NS3 helicase, are examined herein.

Priority

3. The instant application is granted the benefit of priority for the U.S. provisional Application No. 60/194419, filed on April 3, 2001, as requested in the declaration and the first lines of the specification.

Information Disclosure Statement

4. The information disclosure statement (IDS) filed August 31, 2001 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. References AG-AX were not considered because the title of the each of the references was not listed on the IDS. All other documents in said Information Disclosure Statement were considered as noted by the examiner's initials in the attached copy.

Compliance with Sequence Rules

5. The sequence listing, filed in computer readable form (CRF) and paper copy on August 27, 2004, and the statement regarding the sameness of the paper copy and CRF and no new matter, filed on August 27, 2004, have been received and entered. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to **fully** comply with the requirements of 37 C.F.R. § 1.821 through 1.825; Applicants' attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990).

a) On pages 6, 29-31, 34 and 36, the amino acid sequence, SDGK, is disclosed without SEQ ID NO identification.
b) On pages 39-42, in Table 2, and pages 44-45 in Table 5, linear amino acid sequence are disclosed as part of the tables without SEQ ID NO identification.

If the noted sequences are in the sequence listing as filed, Applicants must amend the specification to identify the sequences appropriately by SEQ ID NO. If the noted sequences are

not in the sequence listing as filed, Applicants must provide (1) a substitute copy of the sequence listing in both computer readable form (CRF) and paper copy, (2) an amendment directing its entry into the specification, (3) a statement that the content of the paper and CRF copies are the same and, where applicable, include no new matter as required by 37 C.F.R. § 1.821 (e) or 1.821(f) or 1.821(g) or 1.821(b) or 1.825(d), and (4) any amendment to the specification to identify the sequences appropriately by SEQ ID NO.

Objections to the Specification

6. The specification is objected to because the title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: ---Hepatitis C virus NS3 helicase subdomain I---.

7. The specification is objected to for the improper use of trademarks. The use of the trademarks "SUPERDEX" and "QUICKCHANGE" has been noted in this application. They should be capitalized wherever they appear and be accompanied by the generic terminology. Please see page 32 of the specification for instances of improper trademark use. Correction is required.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks.

8. The disclosure is objected to because of the following informalities. On page 26, lines 27-28, and page 42, line 4, subdomain I of HSV NS3 helicase protein is simultaneously referred to as amino acid residues 181-324 of HSV NS3 helicase protein (which has 144 residues) and as SEQ ID NO: 3; however, SEQ ID NO: 3 in the sequence listing contains 148 residues, not 144, which is confusing. It is unclear what the amino acid sequence of the polypeptide used in crystallization and diffraction experiments is for subdomain I of HSV NS3 helicase protein: SEQ ID NO: 3 or residues 181-324 of HSV NS3 helicase protein. Appropriate correction is required.

9. The Examiner notes that claim 9 contains non-elected subject matter (SEQ ID NO: 4) in the Markush group.

Claim Objections

10. Claims 3-5, 7-8, and 12-13 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The claims are drawn to polypeptide fragments of an HCV helicase protein derived from subdomain I of the HCV NS3 helicase protein (claims 3-5 and 7-8) and crystalline compositions of polypeptide fragments derived from subdomain I (claims 12-13). The instant claims include structural limitations that affect the structure of the subdomain from which the instant polypeptide fragments are derived; however, these structural limitations do not affect the structure of the instant polypeptide fragments. There

is no discernable difference between polypeptide fragments derived from subdomain I of HCV NS3 helicase and polypeptide fragments derived from subdomain I of HCV NS3 helicase with certain structural limitations because the term "derived from" is an indefinite term (see 112, 2nd paragraph rejection).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 1-5, 7-10 and 16-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The abbreviation HCV must be defined upon its first appearance in the claims for clarity. Clarification is required. The Examiner suggests that Applicant use the following language, which incorporates the definition of HCV found on page 1 of the specification, in the first claim in which HCV appears: --- 1. . . . fragment of a hepatitis C virus (HCV) helicase protein ---.

12. Claims 1-5 and 7-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "**an** HCV helicase protein" (emphasis added) is confusing because only one helicase from HCV is known in the art. Examiner suggests using the

phrase ---the hepatitis C virus (HCV) helicase--- in place of the term "an HCV helicase protein". Clarification is required.

13. Claims 1-5, 7-8, 10 and 11-13 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "derived from" as used in claims 1 and 11 is unclear as to the metes and bounds it imparts on the claimed subject matter. Although examples of polypeptides that are "derived from" subdomain I of HCV NS3 helicase protein are outlined in the specification, an explicit definition for what it means for a polypeptide to be "derived from" subdomain I of HCV NS3 helicase protein is not found. In addition, a definition for what it means for a polypeptide to be "derived from" another polypeptide source is not clearly defined in the art with a single meaning. It is not clear what level of similarity must exist for a protein to be considered "derived from" subdomain I of HCV NS3 helicase protein. In addition, it is not clear whether the term "derived from", as used in the claims, refers to polypeptides that are evolutionarily related to subdomain I of HCV NS3 helicase protein or to polypeptides that are made from subdomain I of HCV NS3 helicase protein. Clarification is required.

14. Claims 1-5, 7-8 and 10 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter, which Applicant regards as the invention. The term "structurally sound" is unclear as to the metes and bounds it imparts on the claimed subject matter. A definition for the term "structurally sound" is not disclosed in the specification. In addition, the term "structurally sound" with regards to

polypeptide fragments is not clearly defined in the art with a single meaning. It is not clear whether the term "structurally sound", as used in the claims, refers the chemical or physical stability of a polypeptide fragment, nor is it clear what level of stability or what type of structure must exist for a compound to be considered "structurally sound". Clarification is required.

15. Claims 3-5, 7-8 and 12-13 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter, which Applicant regards as the invention. The claims each refer to specific residues or residue ranges of HCV NS3 helicase (i.e. "amino acids 181 to 324" in claim 3, and "Asp249 and Arg257" in claim 4); however, a SEQ ID NO is not given, which is confusing. Does Applicant mean to claim particular amino acid residues or ranges from SEQ ID NO: 1, 2, 3, 4, 5 or 6? It is not clear exactly which residues Applicant intends to claim without a reference to a SEQ ID NO.

In addition, claims 4-5 and 12-13 are confusing because they are drawn to polypeptides "derived from" HCV helicase having particular amino acid substitutions. Polypeptides that are "derived from" HCV helicase protein can have different amino acid sequences and, thus, do not necessarily contain these particular residue positions. It is not clear how to tell the difference between polypeptides "derived from" HCV helicase having particular amino acid substitutions and polypeptides "derived from" HCV helicase having no amino acid substitutions. Clarification of all the above points is required.

16. Claims 11-13 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter, which Applicant

regards as the invention. The term "subdomain I" is unclear as to the metes and bounds it imparts on the claimed subject matter. An explicit definition of subdomain I is not found in the art or the specification. Does Applicant mean to claim ---subdomain I from HCV NS3 helicase protein---, or subdomain I from another protein? Clarification is required.

17. Claim 15 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter, which Applicant regards as the invention. The claim recites "A crystalline composition comprising . . . structural coordinates", which is confusing because structural coordinates are data, which cannot form a crystalline composition. Does Applicant mean to claim ---A crystalline composition comprising a polypeptide described by the structural coordinates set forth in Table 5---? Clarification is required.

18. Claim 16 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "a buffer for **a** precipitant solution" (emphasis added) is unclear as to the metes and bounds it imparts on the claimed subject matter. Does Applicant mean to claim a buffer for the precipitant solution being claimed, or for any precipitant solution? Clarification is required.

19. Claims 16 and 17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant

regards as the invention. The word "about" as used in the claims as used to describe solution pH, solution temperature, sodium chloride concentration or sodium azide concentration, is unclear as to the metes and bounds it imparts on the claimed subject matter. For example, it unclear whether Applicant means to claim a pH range of between about 4 to about 8, or if Applicant means to claim a pH range with an upper limit of exactly 8.0 and a lower limit of about 4. Moreover, the word "about", as used in the claims, is a relative term that renders the claims indefinite. The word "about" is not defined by the claims, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. For example, it is not clear whether a solution with a pH of 3.5, 3.75 or 3.9 is encompassed by the scope of the claims, and the specification does not provide guidance as to how to interpret the breadth of the term "about". Clarification is required.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

20. Claims 1-5, 7-8, 10-13, and 16-17 are rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instant claims are drawn to polypeptide fragments derived from subdomain I of the HCV NS3 helicase protein (claims 1-5, 7-8 and 10) and crystalline compositions thereof (claims 11-13). While the function

and structure of particular species of said genera of polypeptide fragments are disclosed in the specification, the common functional or structural characteristics of species that describe the genera of polypeptides derived from HCV NS3 helicase are absent.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these (Enzo Biochem 63 USPQ2d 1609 (CAFC 2002)).

The instant specification discloses polypeptides described by SEQ ID NO: 3 (subdomain I of HSV NS3 helicase protein) and specific variants of SEQ ID NO: 3, which are described on pages 5 and 11-12. Applicants have fully described the genus relating to said polypeptides with both sequence identity limitations and functional limitations (i.e. having functional NTP and Mg^{2+} binding sites related to the helicase activity of HCV NS3). However, the genera of the instant claims contains polypeptides fragments with no functional limitations and insufficient

structural limitations (i.e. polypeptide fragments with undefined amino acid sequences). The structural limitation in claim 1 that a polypeptide fragment of an HCV helicase protein must be less than 30kDa is an insufficient structural description for the entire genus of polypeptides. The structural limitations included in claims 3-5, 7-8 and 12-13 do not provide additional structure to the genera of polypeptides fragments that are derived from subdomain I of the HCV NS3 helicase protein because polypeptides that are derived from subdomain I of the HCV NS3 helicase protein can have any amino acid sequence, as previously described (see 112, 2nd paragraph rejection and claim objection). The common structural characteristics of the species in the instant genera that correlate to a functional limitation are also lacking. One of skill in the art would be unable to predict either the function or the structure of other members of the genera by virtue of the instant disclosure. Therefore, claims drawn to the instant genera of molecules are not adequately described.

21. Claim 10 is rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instant claim is drawn to polypeptide fragments derived from subdomain I of the HCV NS3 helicase protein that are in complex with a small molecule HCV helicase inhibitor. While the function and structure of particular species of said genera of HCV helicase inhibitors are known in the art, the structure of each species is not adequately described, nor are the common functional or structural characteristics of species that describe said genera identified.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these (Enzo Biochem 63 USPQ2d 1609 (CAFC 2002)).

The instant specification does not disclose the identity of a specific HCV helicase inhibitor. Some HCV helicase inhibitors are known in the art, however, these species do not represent the entire genus of HCV helicase inhibitors, and Applicants have not disclosed the common structural characteristics of species in the instant genera of HCV helicase inhibitors that correlate to their function. One of skill in the art would be unable to predict either the structure of other members of the genera by virtue of the instant disclosure. Therefore, claims drawn to the instant genera of molecules are not adequately described.

22. Claims 11-15 are rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instant claims are drawn to crystalline compositions of polypeptide fragments derived from subdomain I of the HCV NS3 helicase protein. While the function and structure of particular species of said genera of polypeptide fragments are disclosed in the specification, the structure of each species is not adequately described, nor are the common functional or structural characteristics of species that describe said genera identified.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these (Enzo Biochem 63 USPQ2d 1609 (CAFC 2002)).

In the instant specification, a protein crystal of subdomain I of HCV NS3 helicase protein is described that has space group $P2_1$ and unit cell dimensions a=34.8 Å, b=67.1 Å, c=58.4 Å, α= γ =90°, β=101.3°, and the atomic coordinates shown in Table 5. This crystal is not representative of the claimed genera of crystalline polypeptides derived from subdomain I, comprised of amino acid SEQ ID NO: 3 (claim 14), or described by the structural coordinates in Table 5 (claim 15) because it lacks a correlation of structure and function for the claimed genera. Crystals encompassed by the breadth of the claimed genera have distinct and specific structures described by composition (i.e. polypeptide sequence and cofactors/ligands) and crystal form (unit cell dimensions and space group symmetry). None of claims 11-15 has adequate written description because there is no correlation of structure and function for the claimed genera the crystal forms (space group symmetry and unit cell dimensions). (Examiner notes that while the coordinates in Table 5 have been obtained using a crystal with particular space group and unit cell dimensions, the table, itself, does not include information about space group symmetry and unit cell dimensions of the crystal used). One of skill in the art would be unable to predict the structure of other members of the instant genera by virtue of the instant disclosure. Therefore, claims drawn to the instant genera of crystalline compositions are not adequately described.

23. Claims 1-5, 7-8 and 10-13 are rejected under 35 U.S.C. 112, first paragraph, scope of enablement, because the specification, while being enabling for a polypeptide fragments described by SEQ ID NO: 3 and particular mutants, thereof, does not reasonably provide enablement for the genera of all polypeptide fragments derived from subdomain I of HCV NS3 helicase protein (claims 1-5, 7-8, 10) and all crystalline compositions of polypeptide fragments

derived from subdomain I (claims 11-13). To make all the polypeptide fragments, and crystalline compositions, thereof, included in the scope of these claims would require undue experimentation. The factors to be considered in determining whether undue experimentation is required are summarized above.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

The specification contains a few working examples of polypeptide fragments derived from subdomain I of HCV NS3 helicase: a polypeptide described by SEQ ID NO: 3, and particular mutants, thereof. However, Applicants present no guidance or working examples of

the use of polypeptides that can have such large deviation from the amino acid sequence set forth in SEQ ID NO: 3. The nature of the invention is such that subdomain I of HCV helicase protein functions to bind NTP and Mg^{2+} with relation to HCV helicase activity and must be soluble and monodisperse; and with such a great deviation from the known sequence, the predictability of retaining this same functionality and these physical features becomes extremely low. The predictability of making isolated polypeptides other than those described by SEQ ID NO: 3, and particular mutants, thereof, which also maintain the function of binding NTP and Mg^{2+} and are soluble, can be increased by comparing the sequences of a genus of known NTP, Mg^{2+} helicase binding subdomains to SEQ ID NO:3 and identifying important/conserved residues. However, the state of the prior art is such that a comparison of a sufficient number of sequences of these NTP, Mg^{2+} helicase binding subdomains to the disclosed SEQ ID NO: 3 cannot be performed. Moreover, the instant claims are drawn to polypeptide sequences that can have less than 50% sequence identity to SEQ ID NO: 3. Such enormous breadth and unpredictability render the instant claims not enabled to the full extent of their scope without undue experimentation.

24. Claims 11-15 are rejected under 35 U.S.C. 112, first paragraph, scope of enablement, because the specification, while being enabling for protein crystals with space group $P2_1$, unit cell dimensions a=34.8 Å, b=67.1 Å, c=58.4 Å, $\alpha = \gamma = 90°$, $\beta = 101.3°$, and the atomic coordinates shown in Table 5, does not reasonably provide enablement for all crystalline compositions of polypeptide fragments from subdomain I of HCV NS3 helicase protein or polypeptide fragments described by SEQ ID NO: 3 or the coordinates in Table 5. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make

the invention commensurate in scope with these claims. To make the claimed invention to the full extent of its scope would require undue experimentation. The factors to be considered in determining whether undue experimentation is required are summarized above.

The instant specification teaches the crystallization of a specific sequence of subdomain I of HCV NS3 helicase protein (SEQ ID NO: 3) under specific conditions to yield a particular crystal form (defined by space group and unit cell dimensions). In order to make crystalline compositions of the polypeptides encompassed by the scope of the claims, the following must be clear: the preparation and chemical composition of the molecules to be crystallized, and the crystallization conditions, including methods and reagents used. Applicants present no guidance or working examples of the preparation and crystallization of polypeptides that deviate so greatly from the instant amino sequence. The nature of the invention is such that small changes in any of the aforementioned factors can change the unit cell dimensions and space group symmetry of a crystal dramatically (Giege, 1994, see PTO-892; McPherson, 1995, see PTO-892); therefore, precise instruction about how to make the protein crystals is required. The state of the prior art is such that crystallization conditions for HCV NS3 helicase subdomain I or fragments, thereof, are unknown. Such enormous breadth and unpredictability render the instant claims not enabled to the full extent of their scope without undue experimentation.

25. Claim 16 is rejected under 35 U.S.C. 112, first paragraph, scope of enablement, because the specification, while being enabling for precipitant solutions that crystallize particular fragments of subdomain I HCV helicase fragments, does not reasonably provide enablement for the genus of precipitant solutions that precipitate or crystallize any compound, including any fragment of subdomain I HCV helicase. The specification does not enable any person skilled in

the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. To make the claimed invention to the full extent of its scope would require undue experimentation. The factors to be considered in determining whether undue experimentation is required are summarized above.

In Example 14 on page 42, the specification discloses a particular precipitant solution containing a fragment of subdomain I HCV NS3 helicase polypeptide fragment described by a specific sequence that crystallizes said polypeptide fragment. Applicants present no guidance or working examples of precipitant solutions used for any other purpose than crystallizing HCV NS3 helicase fragment polypeptides; and Applicants present few working examples of precipitant solutions for crystallizing HCV NS3 helicase fragments within in the breadth of pH, salt, type of precipitant, and helicase fragment structure encompassed by the claims. The nature of the invention is such that determining the parameters that crystallize or precipitate any HCV NS3 polypeptide fragment is difficult (Giege, 1994, see PTO-892; McPherson, 1995, see PTO-892). In addition, the state of the prior art is such that precipitant solutions that crystallize HCV NS3 helicase subdomain I or fragments, thereof, are unknown. Such enormous breadth and unpredictability render the instant claims not enabled to the full extent of their scope without undue experimentation.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

26. Claims 1-5 and 7-8, 10-13 and 15 are rejected under 35 U.S.C. § 101 because the claimed inventions are directed to non-statutory subject matter. The claims, as written, do not sufficiently distinguish over the polypeptide fragments as they naturally exists because the claims do not particularly point out any non-naturally occurring differences between the claimed products and the naturally occurring products. The claims are drawn to a polypeptide fragments (1-5 and 7-14) and crystalline compositions of polypeptide fragments (claims 11-13 and 15). Although polypeptides and crystalline compositions, thereof, may be created in the laboratory, they may also occur naturally (Van der Klei, 1991, Alvares, 1992, see PTO-892). (Claims 9 and 14 are excluded from the rejection because they are drawn to polypeptides described by SEQ ID's which contain engineered, non-naturally occurring amino acid sequences). It is not clear that the polypeptides in the claims and crystalline compositions, thereof, are only those engineered in the laboratory. In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. See Diamond v. Chakrabarty, 447 U.S. 303, 206, USPQ 193 (1980). The claims should be amended to indicate the hand of the inventor, e.g. by insertion of "isolated" or "purified" as taught by pages 27 of the specification. See M.P.E.P. § 2105.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

27. Claims 1-5, 7-8, 10-13 and 16 are rejected under 35 U.S.C. § 102(a) as being anticipated by Benz *et al.* (see PTO-892) as evidenced by PGPUBS 20040253577 (see PTO-892). The instant claims are drawn to a polypeptide fragment derived from subdomain I of the HCV NS3 helicase protein, which is less than 30 kDa, soluble, monodisperse and stable in buffered solution (claim 1), optionally suitable for use in nuclear magnetic resonance (claim 2), optionally derived from subdomain I having particular structural features (claims 3-5, 7-8 and 10); to a crystalline composition containing a polypeptide fragment derived from subdomain I of HCV NS3 helicase protein (claim 11), optionally derived from subdomain I having particular structural features (claims 12-13); and to a precipitant solution which has a pH of 4-7 and a temperature of 1-26°C, which contains an HCV helicase fragment, from 5-35% weight to volume of a precipitant compound, from 1 to 1000 mM of a salt, and a buffer.

Benz *et al.* teach the isolation and crystallization of a fragment of translation initiation factor 4A (eIF4A), which is a DEAD-box protein that, with EiF4B, has RNA helicase activity (see page 671). The eIF4A fragment purified and crystallized by Benz *et al.* is less than 30 kDa (amino acids 9-232 of eIF4A) and is monodisperse (see pages 672-673). The eIF4A fragment taught by Benz *et al.* was concentrated to 20mg/mL in Tris buffered solution in preparation for crystallization of the properly folded molecule, and, thus, can be considered both soluble and stable in buffered solution (see page 678, column 2). Benz *et al.* teach crystallization of the eIF4A fragment in a solution of 20% PEG 8000 (a precipitant), 200 mM ammonium sulfate (a salt) and 0.1 M MES (a buffer) at 20°C and pH 4.8.

The eIF4A fragment taught by Benz *et al.* can be considered suitable for NMR because it is monodisperse, soluble at high concentration and has a small molecular weight. The structural limitations set forth in claims 3-5, 7-8, 10 and 12-13 cannot be considered real limitations to the claims for the reasons previously set forth in the claim objections. In the broadest reasonable interpretation of the claims, eIF4A can be considered a fragment derived from subdomain I of the HCV NS3 helicase protein (as required by claims 1-5, 7-8, 10-13) or an HCV helicase fragment (as required by claim 16) because Applicant has not set forth an explicit definition for either of these terms (see 112, 2nd paragraph rejection) and, like eIF4A, HCV NS3 helicase is a DEAD box protein with helicase activity (see page 3, PGPUBS 20040253577). Therefore, the polypeptide taught by Benz *et al.* embodies every aspect of claims 1-5, 7-8, 10-13 and 16.

28. Claims 11-13 are rejected under 35 U.S.C. § 102(b) as being anticipated by Kim *et al.* (see PTO-892). The instant claims are drawn to crystalline compositions of polypeptide fragments derived from subdomain I of HCV NS3 (claim 11), optionally derived from subdomain I having particular structural features (claims 12-13);.

Kim *et al.* teach a crystalline composition of HCV NS3 helicase in complex with a single stranded DNA oligonucleotide (see page 98). In broadest reasonable interpretation of the claims, NS3 helicase can be considered to be derived from subdomain I of HCV NS3 helicase because it contains subdomain I of HCV NS3 helicase and the structural limitations in claims 12-13 are not real limitations, as previously described . Therefore, Kim *et al.* have anticipated every aspect of claims 11-13.

Other Art for Comment/Examiner's Suggestions

The following are cited to complete the record:

a) Kim *et al.* (see PT0-892) teach the purification and crystallization of the RNA helicase domain of hepatitis C virus; however, they do not teach fragments of the RNA helicase domain smaller than 30 kDa or crystallization conditions in the pH range of 4-7. In addition, the structural coordinates for HCV RNA helicase taught by Kim *et al.* do not appear to be exactly the same as those set forth in Table 5 of the instant application, to the extent that can be assessed by the Examiner with the tools available. Lastly, the sequence taught by Kim *et al.* does not comprise the N-terminal 4 amino acids of SEQ ID NO's : 3, 5 and 6.

Conclusion

29. Claims 1-5 and 7-17 are rejected for the reasons identified in the numbered sections of the Office action. Applicants must respond to the objections/rejections in each of the numbered sections in the Office action to be fully responsive in prosecution.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lindsay Odell whose telephone number is 571-272-3445. The examiner can normally be reached on M-F, 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

KATHLEEN KERR, PH.D.
PRIMARY EXAMINER

Lindsay Odell, Ph.D.
April 29, 2005